Regulation of Prescription Drug Promotion

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Overview

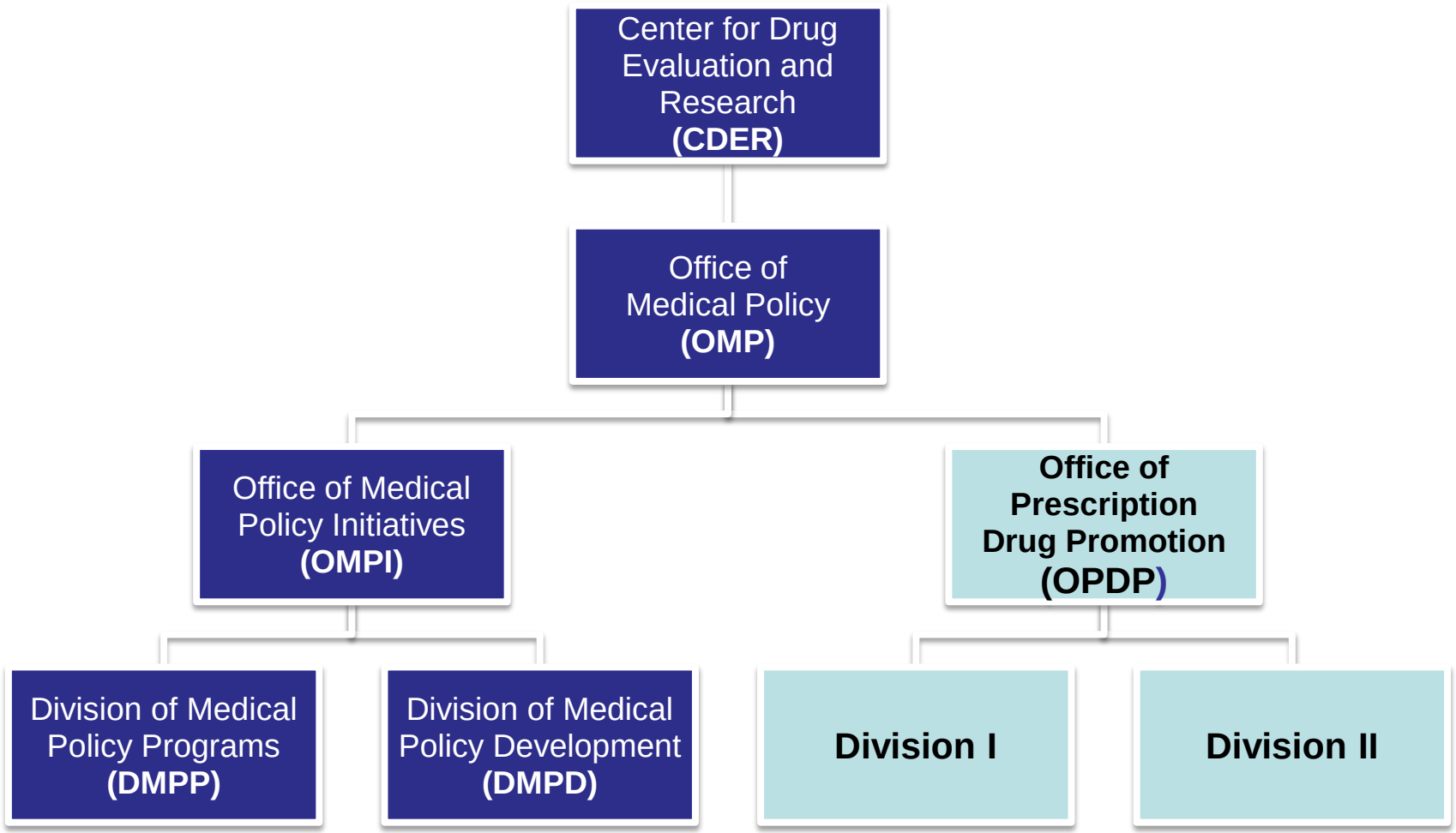
- Office of Prescription Drug Promotion (OPDP)
  - Who We Are
  - What We Do
  - What We Regulate
- Regulatory authority
- Advertising and promotion
- Operational role

OPDP's Mission

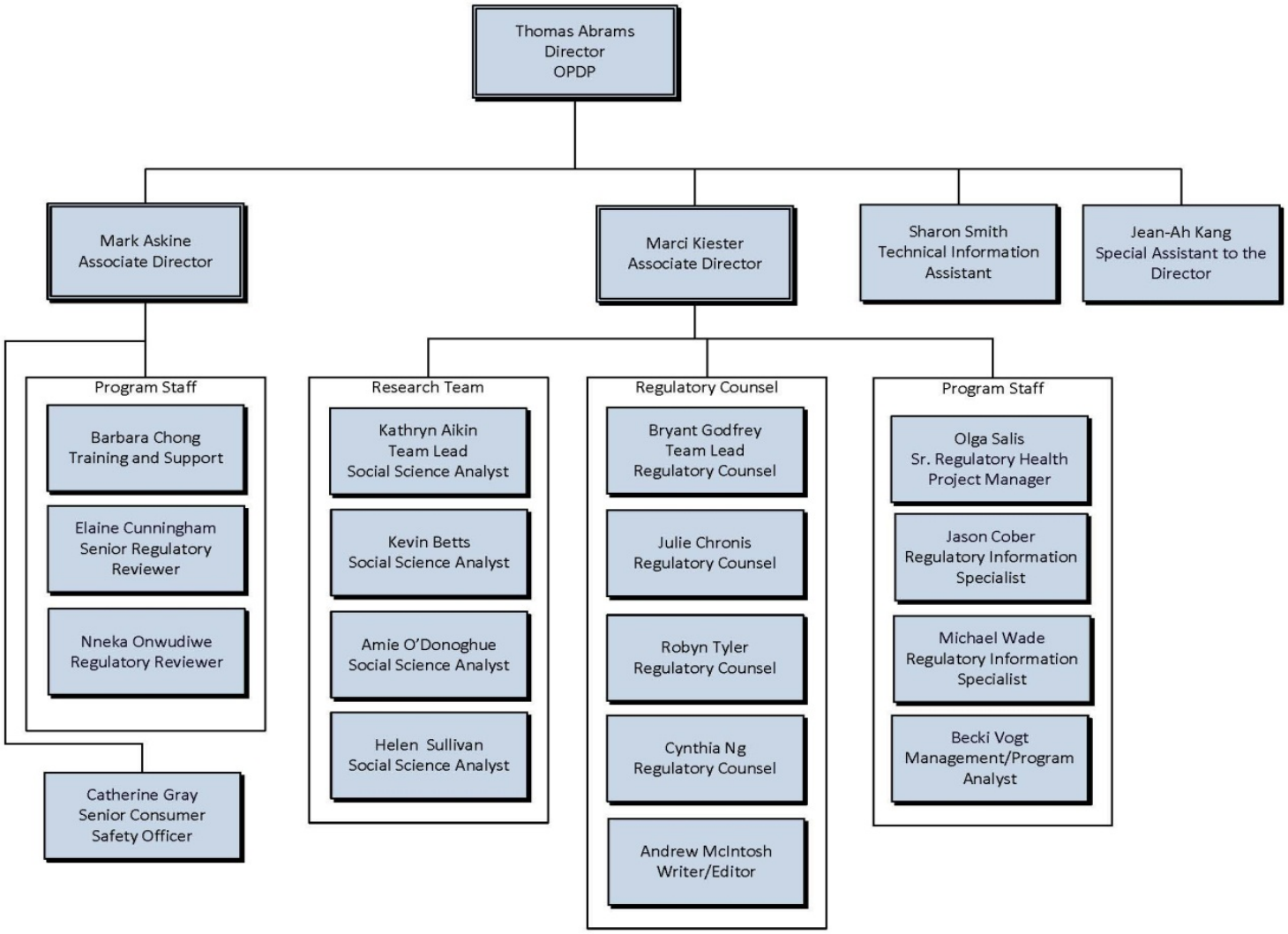
- To protect the public health by assuring prescription drug information is truthful, balanced and accurately communicated.

- To guard against false and misleading advertising and promotion through comprehensive surveillance, enforcement, and educational programs

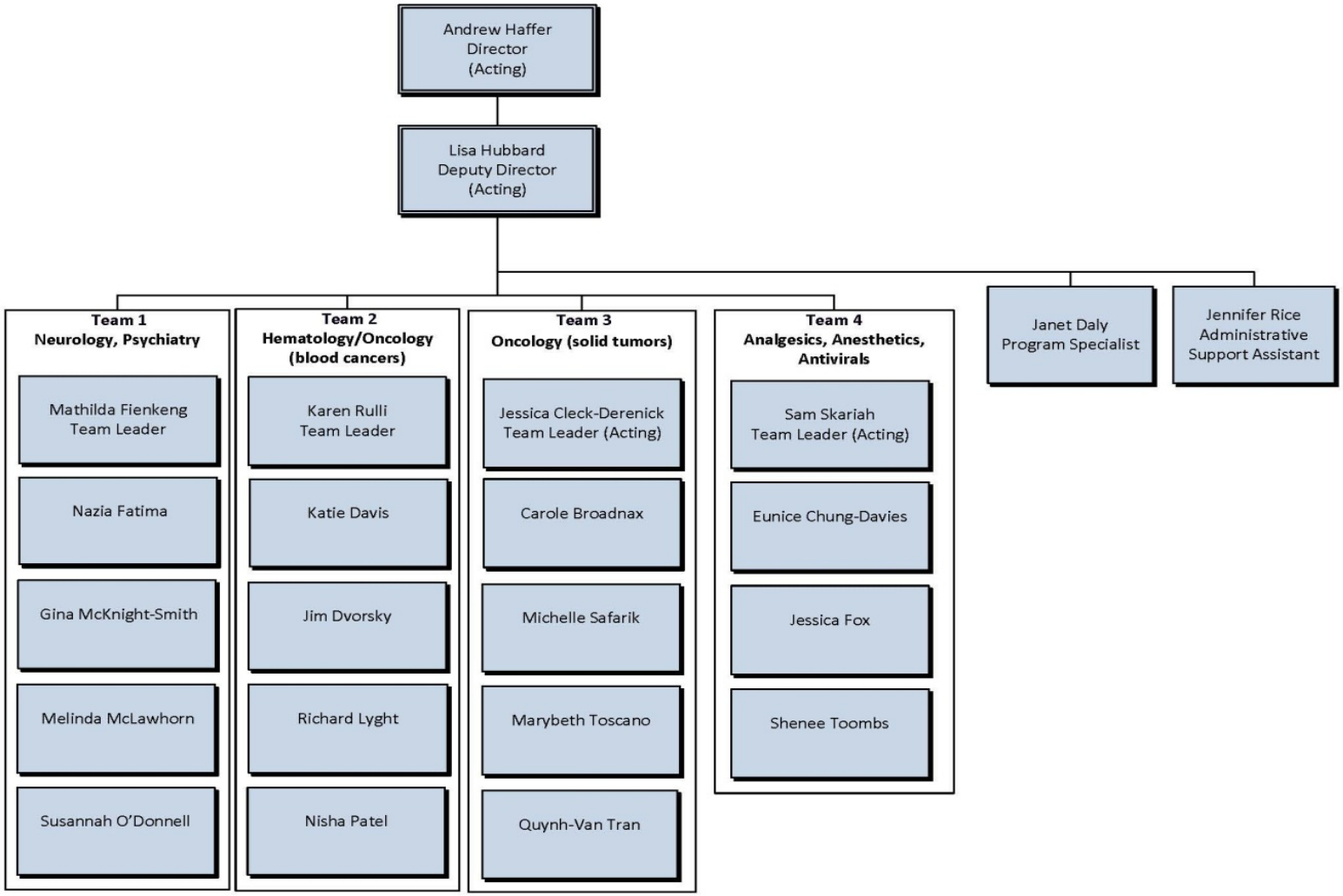
CDER → OMP → OPDP



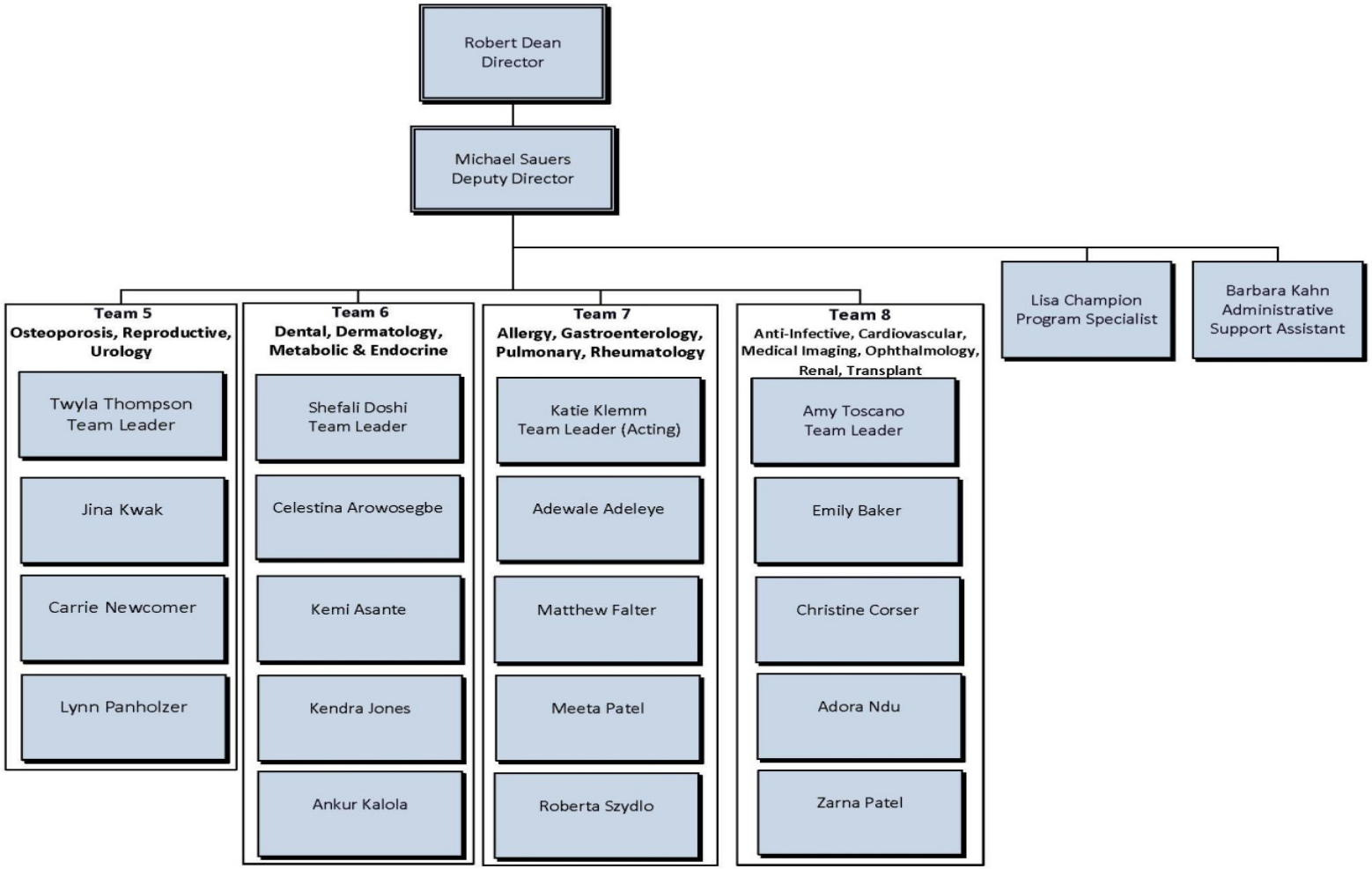
Office of Prescription Drug Promotion/Immediate Office (OPDP/IO)



OPDP – Division I



OPDP – Division II



What Does OPDP Regulate?

- Written and printed prescription drug promotional materials made by the company which include:
  - TV and radio commercials
  - Sales aids, journal ads, and patient brochures
  - Drug websites, e-details, webinars, Epocrates, and email alerts

- Oral Presentations made by representatives of the company which include:
  - Sales Reps
  - Hired Spokespeople
  - Medical Science Liaisons

DTC Myths and Misperceptions

- FDA “legalized” DTC advertising in the late 1990’s
- Industry spends most of its advertising budget on DTC advertising
- FDA has the authority to ban DTC advertising
- FDA can restrict DTC advertising to certain types of products
- FDA approves DTC ads
- FDA regulates “good taste”

Federal Food, Drug and Cosmetic Act (FFD&C Act)

- Code of Federal Regulations (CFR)
  - 202.1 - Prescription Drug Advertising
  - 312.7 - Preapproval Promotion
  - 314.550 - Subpart H, Accelerated Approval
  - 601.40 - Subpart E, Accelerated Approval for Biologics

Regulatory Authority

Post-Approval Regulations located in 21 CFR 314.81(b)(3):

- Require the submission of all promotional materials at the time of initial dissemination or publication
- Must include Form FDA 2253 and current PI
- OPDP receives >80K submissions per year
- OPDP does not generally "pre-clear" promotional materials

Categories of Promotional Materials

Categories of Promotional Materials

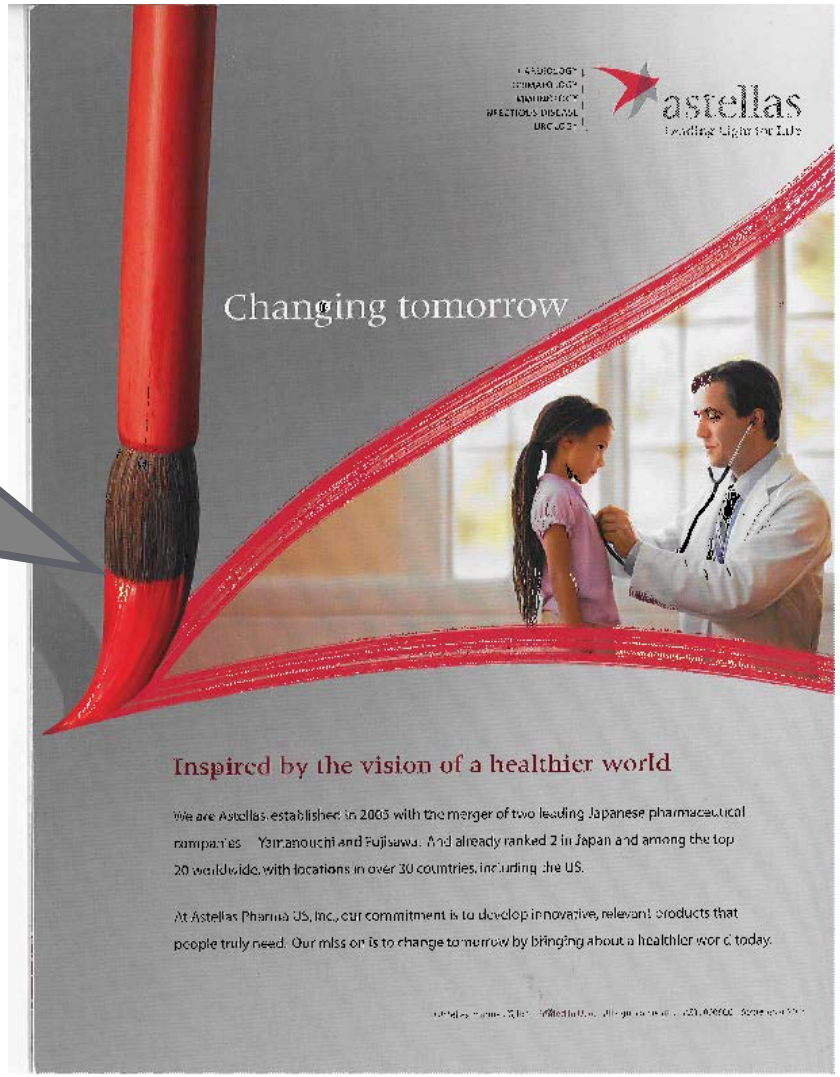
	Accompanied By	Dissemination	Examples of Types of Materials
Advertisements	Brief Summary	Magazines, journals, periodicals, newspapers Broadcast: TV, radio and telephone communication systems	Journal ads, TV ads & radio ads
Promotional Labeling	Product Labeling (PI)	Supplied by manufacturer, distributor, packer or any party acting on the sponsor's behalf	Brochures, sales aids, mailing pieces & slide decks

Categories of Promotional Materials

Institutional Ad

Includes information such as
- **-Company name**
- **-Area of Research**

May not mention any drug names

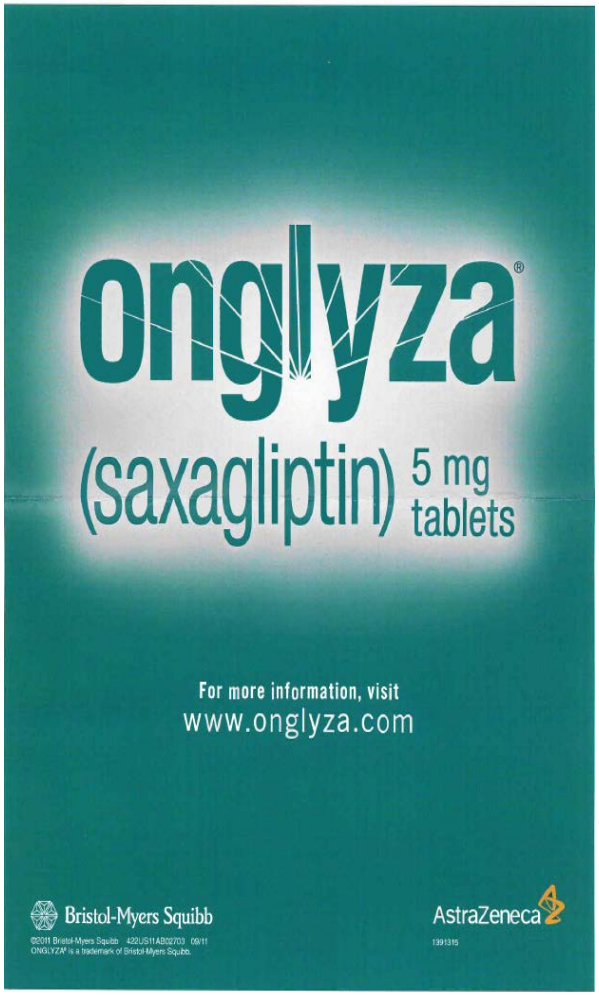


Categories of Promotional Materials

Help Seeking/Disease Awareness Communications May:

- **Discuss a medical condition or disease state**
- **Include company name**
- **Not include drug name**

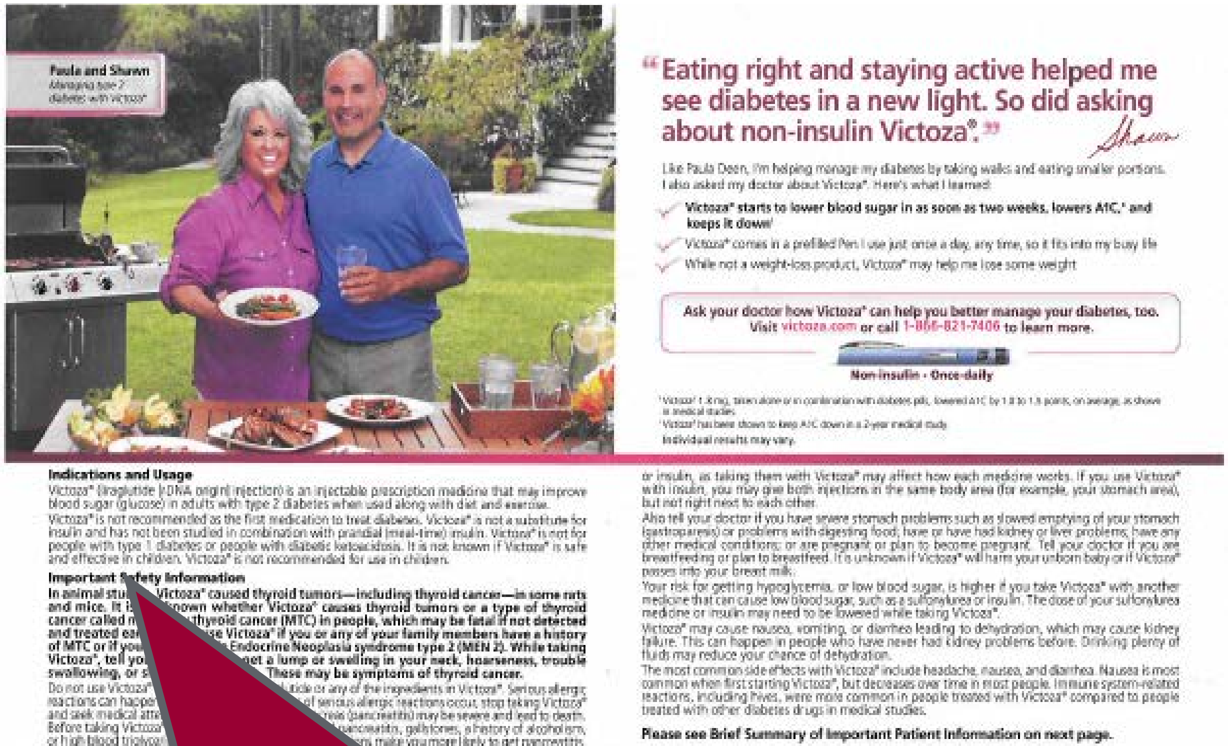
Categories of Promotional Materials



Reminder Ad

1) Includes proprietary & established name
2) May call attention to drug name but may NOT contain any representation or suggestion relating to the advertised drug
3) May include dosage form, package contents, price, name of manufacturer, packer or distributor
4) Not permitted for drugs with a boxed warning

Categories of Promotional Materials



Full Product Ad

-Include representation or suggestion relating to the advertised drug product

-Must include a balanced risk presentation ("fair balance")

-Must include the Brief Summary or PI

Brief Summary

Categories of Promotional Materials: DTC Broadcast Ad Nuances

- "**Major Statement**"
  - Information relating to the major side effects and contraindications
- "**Adequate Provision**"
  - Recognizes the inability of broadcast advertisements of reasonable length to present and communicate this information effectively
  - Provides for dissemination of the full prescribing information for the drug
    - Toll-free phone number
    - Simultaneously running magazine ad
    - Reference to healthcare provider
    - Website

What does OPDP do?

- Advice to industry
- Advice within FDA
- Guidances and Policy Development
- Research
- Surveillance and Enforcement

Advice to Industry

- Provide comments on DRAFT promotional materials (VOLUNTARY in most cases)
  - Launch materials for new drugs or new indications
  - Direct-to-consumer (DTC) broadcast ads
  - Non-launch materials
- Pre-submission required for certain drugs
  - (e.g., Subpart H/Subpart E “accelerated approval”)

Language in Approval Letters

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm

Language in Approval Letters (Accelerated Approval)

PROMOTIONAL MATERIALS

Under 21 CFR 314.550, you are required to submit, during the application pre-approval review period, all promotional materials, including promotional labeling and advertisements, that you intend to use in the first 120 days following marketing approval (i.e., your launch campaign). If you have not already met this requirement, you must immediately contact the Office of Prescription Drug Promotion (OPDP) at (301) 796-1200. Please ask to speak to a regulatory project manager or the appropriate reviewer to discuss this issue.

As further required by 21 CFR 314.550, submit all promotional materials that you intend to use after the 120 days following marketing approval (i.e., your post-launch materials) at least 30 days before the intended time of initial dissemination of labeling or initial publication of the advertisement. We ask that each submission include a detailed cover letter together with three copies each of the promotional materials, annotated references, and approved package insert (PI)/Medication Guide/patient PI (as applicable).

Launch Advisories

- First 120 days of marketing to public
- Prior to first use in public domain
  - Should not disseminate same/similar claims while review is pending
- Applies to new drug, indication, delivery system, formulation, or route of administration
- Certain types of materials
    - e.g., press releases, TV ads, sales aids, patient brochures, print ads, websites
    - Size limits
      - Sales aids/patient brochures/websites: 12 pages
      - Print ads: 4 pages
- Goal timeline: 45 calendar days (minus time required for medical officer consult)

Submitting Materials for Advisory Comments

- Claims or presentations not in the public domain
- Can bundle together into one submission (exception is TV ads)
  - Consolidate into single submission rather than sending the materials piecemeal in several submissions over the course of a few days/weeks.
  - submit professional and consumer materials separately
  - Separate launch core vs. launch non-core vs. non-launch
- If submitting professional and DTC core launch materials around same time, submit both on same day (same 45-day goal)
- Submit materials in hardcopy in triplicate unless otherwise specified
  - TV ads: 17 copies if first time on TV; 10 copies otherwise
- Do NOT include Form FDA-2253 or 356H

Submitting Materials for Advisory Comments

- Cover letter
  - state request for advisory comments, with contact information (name, title, address, phone, fax, and email)
  - "Request for Advisory Comments" in subject line
  - List each promotional material individually
  - Include material type (2253 code) for each piece
- Draft promotional materials <u>including annotations</u> to references
- Annotated supporting references
- Annotated current Approved Package Insert/Medication Guide/Patient Package Insert

Advice within FDA

Provide consultation on:

- Prescribing information
- Cartons and product labels
- Medication Guides
- Patient Package Inserts (PPIs)
- Dear Healthcare Provider letters
- Pharmacoeconomics, health-related patient-reported outcome protocols

Surveillance and Enforcement

Surveillance

- Review materials submitted to OPDP at time of initial dissemination
  - Sponsors must submit on Form FDA 2253
  - OPDP receives ~80,000 unique pieces each year
- Conferences
- Complaints
  - Healthcare professionals
  - Consumers
  - Competitors

Compliance with FFD&C Act

- Must be consistent with approved product labeling
- Must be supported by substantial evidence
- Must not be false or misleading
- Must have balance between efficacy and risk information
- Must reveal all material information

What is False or Misleading?

- Better or more effective than has been demonstrated by substantial evidence
- Safer (fewer side effects, lower severity) than has been demonstrated by substantial evidence
- Comparative claims (better or safer than other products) without substantial evidence
- Misleading presentation of data

Limitations to Surveillance

- Regular surveillance activities include:
  - Monitor promotional materials sent in via 2253s
  - Monitor Medical Convention Exhibit Halls
  - Review complaints

- Limited ability to monitor certain types of drug promotion: physician offices and industry-sponsored dinner/lunch programs
  - Verbal statements from drug reps or company-paid speakers
  - Home-made promotional materials not submitted to FDA

Bad Ad Program

- FDA-sponsored outreach program designed to educate HCPs about the role they can play in helping FDA ensure that prescription drug advertising and promotion is truthful and not misleading

- When HCPs recognize misleading drug promotion, they can help put a stop to it by reporting it to FDA

  - Call
    - **877-RX-OPDP (877-793-3622)**
  - Email
    - **BadAd@fda.gov**

Report Misleading Rx Drug Promotion

U.S. Department of Health and Human Services

U.S. Food and Drug Administration

The prescriber can play an important role in ensuring that prescription drug advertising and promotion is truthful by recognizing and reporting misleading drug advertising and promotion.

BadAd@fda.gov
badad
Food and Drug Administration FDA

Prescription drug advertising must:

- Be accurate
- Balance the risk and benefit information
- Be consistent with the prescribing information approved by FDA
- Only include information that is supported by strong evidence

What types of promotion does the Office of Prescription Drug Promotion (OPDP) regulate?

- Sales representative presentations
- Speaker program presentations
- TV and radio advertisements
- All written or printed drug promotional materials

OPDP does not regulate promotion of:

- Over-the-Counter Drugs
- Dietary Supplements
- Medical Devices

Common Violations:

- Omitting or downplaying of risk
- Overstating the effectiveness
- Promoting off label, or unapproved, uses
- Misleading drug comparisons

BadAd@fda.gov • 855-RX-BADAD

Enforcement

- Untitled Letters/Notices of Violation
- Warning Letters
- Injunction/Consent decree
- Seizures/Criminal action
- Civil and monetary penalties

http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/WarningLettersandNoticeofViolationLetterstoPharmaceuticalCompanies/default.htm

Enforcement Actions

- Mitosol® (mitomycin for solution) Untitled Letter

- Zovirax® (acyclovir) Cream 5% Untitled Letter

Mitosol®(mitomycin for solution)

- Indication: adjunct to ab externo glaucoma surgery
- Contraindications: hypersensitivity and use in pregnancy
- W&P: cell death, post-operative hypotony, lenticular change and cataract formation in phakic patients
- Common AEs: hypotony, hypotony maculopathy, blebitis, endophthalmitis, vascular reactions, corneal reactions, and cataract

Mitosol: Violative Piece

Mitosol Untitled Letter: Violations Cited

- Omission and Minimization of Risk Information/Omission of Material Facts
  - Makes claims about safety, effectiveness, and use, but fails to disclose full approved indication or any risk information
  - Makes claims regarding dosing benefits, but fails to present dosing information material to safe use of drug
    - "Remove the Variables" in conjunction with the word "Dosing"
    - "Assured Dosing – Yes"
    - Mitosol requires reconstitution and reconstituted product is then fully saturated on sponges and applied and kept on treatment area for 2 minutes. Also must be used within one hour of reconstitution

Zovirax® (acyclovir) Cream 5%

- Indication: Treatment of recurrent herpes labialis (cold sores) in adults and adolescents (> 12 years old)
- Contraindications: Hypersensitivity
- Precautions: cutaneous use only (not in eye or inside the mouth or nose); potential for irritation and contact sensitization; effect not established in immunocompromised patients.
- Common AEs: dry lips, desquamation, dryness of skin, cracked lips, burning skin, pruritus, flakiness of skin, and stinging on skin

Zovirax: Violative Piece

ZOVIRAX® (ACYCLOVIR) OINTMENT 5% | ZOVIRAX® (ACYCLOVIR) CREAM 5%

CORIA

This site is intended for healthcare professionals within the United States only.

ZOVIRAX® Ointment Full Prescribing Information | ZOVIRAX® Cream Full Prescribing Information | Important Safety Information | Consumer Site | Contact Us

- ZOVIRAX® Ointment
- **ZOVIRAX® Cream**
- Patient Materials
- Rebate Information
- Home

PROVEN EFFECTIVE AT ANY STAGE*

Even When Therapy Is Initiated Late[3]

Progression of an untreated herpes lesion		Begin treatment with ZOVIRAX® Cream[2,3]	Begin treatment with Valtrex®[3]
STAGE 1 Prodrome or early[4,5]	Tingling, burning, pain, or itching sensation is present	✓	✓
STAGE 2 Papule or swelling[4]	Small red bumps begin to blister	✓	No Data†
STAGE 3 Vesicle or blistering[4]	Blisters fill with liquid, forming full-scale cold sore	✓	No Data†
STAGE 4 Ulcer or weeping[4]	Blisters rupture	✓	No Data†
STAGE 5 Crust or scabbing[4]	The lesion collapses. A yellowish crust forms and falls away	✓	No Data†
STAGE 6 Healing[4]	Redness and irritation fade, returning the cold sore virus to a dormant state	✓	No Data†

ZERO IN WITH EFFICACY

Therapy should be initiated as soon as possible following onset of signs and symptoms.

*"Early" lesion stage is defined as prodrome or erythema. "Late" stages include papule, vesicle, or ulcer.
†There are no data on the effectiveness of treatment with Valtrex® initiated after the development of clinical signs of a cold sore (eg, papule, vesicle, or ulcer) in the Valtrex® full prescribing information.[1]
Trademarks are the property of their respective owners.

TARGETED. TOPICAL. ANTIVIRAL.

ZOVIRAX® (acyclovir) Cream 5% is indicated for the treatment of recurrent herpes labialis (cold sores) in adults and adolescents (12 years of age and older).

ZOVIRAX Cream should be applied 5 times per day for 4 days. Therapy should be initiated as early as possible following onset of signs and symptoms (i.e., during the prodrome or when lesions appear). For adolescents 12 years of age and older, the dosage is the same as in adults.

Important Safety Information

ZOVIRAX® Cream is intended for cutaneous use only and should not be used in the eye or inside the mouth or nose. ZOVIRAX® Cream has a potential for irritation and contact sensitization. In clinical trials, the most common adverse reactions at the site of topical application occurred in less than 1% of patients and included dry lips, desquamation, dryness of skin, cracked lips, burning skin, pruritus, flakiness of skin, and stinging on skin. ZOVIRAX® Cream does not prevent transmission of HSV infections, and its effect has not been established in immunocompromised patients.

ZOVIRAX® Cream is available by prescription only.

Please click here for full Prescribing Information.

This site is intended for healthcare professionals within the United States only.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

Zovirax Untitled Letter: Violations Cited

- Overstatement of Efficacy
  - "PROVEN EFFECTIVE AT ANY STAGE, Even When Therapy Is Initiated Late"
  - Suggests Zovirax proven effective during stages 4 through 6 (ulcer or weeping, crust or scabbing, or healing stages)
  - According to the PI:
    - "Therapy should be initiated as early as possible following onset of signs and symptoms (i.e., during the prodrome or when lesions appear)"
    - 2 pivotal clinical trials: patients instructed to initiate treatment within 1 hour of signs or symptoms of lesion

Zovirax Untitled Letter: Violations Cited

- Unsubstantiated Superiority
  - Zovirax vs. Valtrex
    - Presentations suggests Zovirax clinically superior to Valtrex due to extended timeframe of treatment initiation

Contact Us

- Phone: 301-796-1200
- Fax: 301-847-8444 or 8445

- http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm090142.htm

Where to Submit Materials

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266